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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,949	02/19/2002	Ebrahim Zandi	064189-0501	6542

38706 7590 09/02/2009

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
09/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/079,949	ZANDI ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-7,17-19,21-23 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5-7,17-19,21-23 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/09 has been entered.

Claims 1, 3, 4, 8-16, 20 and 24-41 have been canceled. Claims 2, 5-7, 17-19, 21-23, and 42 are still at issue and are present for examination.

Applicants' arguments filed on 7/28/09, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 5-7, 17-19, 21-23 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothwarf et al. (Reference C27 of Applicant's PTO-1449) in view of Traincard et al. and Epinat et al.

Rothwarf et al. teach the co expression of IKKα, IKKβ and IKKγ genes in a eukaryotic host by inserting the genes encoding each subunit fused to a tag (HA, FLAG or 6-His) into a mammalian expression vector, growing the host cell, lysing the host cell, and immunoprecipitating the IKK complexes. The only difference in the methods taught by Rothwarf et al. to the methods of the instant claims is that in the instant claims the expression host used is yeast.

Traincard et al. teach that within eukaryotic organisms, no homologs of any of member of the NF-κB signaling system (clearly disclosed as including Rel/NF-κB subunit genes, IκB subunit genes and IKK genes) has been found within the genomes of *C. elegans* or *Saccharomyces cerevisiae* both of which were fully sequenced genomes at the time of publication of Traincard et al.

Epinat et al. teach that yeast is a convenient host for the reconstitution of the NF-κB system since it does not contain any endogenous NF-κB activity (see page 603) and that the reconstituted system provides an easy assay for testing stimuli or specific proteins that are postulated to be involved in NF-κB signaling (see page 609). Epinat et al. further suggest that yeast lack any endogenous IKK activity (see Figure 4 and page 609) and teach expression vectors for the recombinant expression of genes involved in the NF-κB signaling pathway in yeast cells under the control of both constitutive promoters such as the *ADH1* promoter and inducible promoters such as the *GAL1* promoter. The yeast expression vectors comprise selection markers such as the *URA3* or *LEU2* genes.

As the IKK complex is well known to be the part of the NF-κB signaling pathway responsible for IκB phosphorylation and as both Traincard et al. and Epinat et al. clearly suggest that yeast lack any endogenous IKK activity (as Traincard et al. teach that no IKK homologous genes were found in the yeast genome and Epinat et al. showed that an expressed IκB protein could not be phosphorylated in yeast even under similar stimuli to those known to induce IκB phosphorylation in mammals) and as yeast are well known in the art to be the workhorse organism for the expression of eukaryotic proteins of interest, it would have

been obvious to one of ordinary skill in the art to reconstitute the IKK complex in a yeast host cells by expressing the IKK subunit genes of Rothwarf et al. in yeast using any known yeast expression vector or yeast expression vectors as taught by Epinat et al.

Applicants argue that Rothwarf et al. does not teach that the IKK complex can be activated by NIK or MEKK1 in yeast systems because yeast lack the upstream regulatory elements believed necessary for expression and activation of the complex. Applicants argue that for NIK to active IKK-α/β, all of the following must occur: 1) NIK is activated, 2) NIK's cofactor is present and binds to NIK, and 3) NIK's substrate, IKK, is in a suitable condition for activation and the molecular mechanisms by which MEKK1 activates IKK is even less well understood and as of the effective filing date, it was suspected that MEKK1 does not directly activate IKK. However, this is not persuasive because the references directly cited by Rothwarf et al. in support of the statement that the IKK complex can be phosphorylated by the NIK and MEKK1 proteins to produce an active complex (i.e., Ling et al., PNAS 95:3792 and Nakano et al., PNAS 95:3537) evidence that overexpression of NIK or MEKK1 in mammalian cells with the IKK complex is not necessary for phosphorylation and activation of the IKK complex by these

proteins. Ling et al. directly show that ***in vitro*** (i.e., in the absence of any cellular context) NIK phosphorylates IKK-α on Ser176 and IKK-β on Ser177 (i.e., within the T-loop of IKK-α and IKK-β). See particularly page 3793 of Ling et al. Thus one could clearly use NIK exactly as prepared by Ling et al. to activate IKK complex expressed in yeast cells. Similarly, Nakano et al. explicitly states that "Our present data are consistent with previous findings that MEKK1 was present in the IKK complex and **exogenously added KEKK1 stimulated kinase activity of the IKK complex *in vitro***" [emphasis added] on page 3541 and thus one could use exogenously added MEKK1 to activate IKK complex expressed in yeast cells.

Applicants argue that U.S. Patent No. 6,864,355 does not teach that IKK complex can be autophosphorylated and activated but instead that autophosphorylation serves to down-regulate TNFα-induced IKKβ activity and make it refractory to TNFα-induced signals. However, this statement ignores other teachings of the '355 patent. Column 24, line 53 - column 25, line 40 makes it clear that IKKβ (1-644) [which lacks the C-terminal autophosphorylation site and the NEMO (IKKγ) binding site] was not autophosphorylated at all and did not induce NF-κB activity, IKKβ (1-733) [which includes the C-terminal autophosphorylation site but lacks the NEMO (IKKγ) binding site]

had increased autophosphorylation and NF-κB activity compared to wild type IKKβ but the activity was not further enhanced by TNFα while IKKβ (1-744) [which includes the C-terminal autophosphorylation site and the NEMO (IKKγ) binding site] had identical autophosphorylation and NF-κB activity as wild type but the NF-κB activity and further autophosphorylation was further inducible by TNFα. These teachings make it clear that there is one or more autophosphorylation sites that are dependent on the presence of NEMO but that the presence of NEMO in some way prevents phosphorylation of these sites in the absence of induction by TNFα or other inducers. Clearly this additional autophosphorylation is necessary for activation and the presence of IKKγ is necessary for it to be active only in the presence of inflammatory stimuli instead of constitutively active as IKKβ (1-733) is.

Finally applicants argue that the examiner stated that production of substantially homogenous and biologically functional IKK protein is expected because they {not clear what they refers to here but presumably activation} are inherent functions of the α, β, and γ subunits. However, this is not what was said. What was said was that knowledge that the IKKγ subunit regulates the autophosphorylation of the IKK complex would not have been necessary for an expectation of production

of substantially homogenous and biologically functional IKK protein in yeast as a skilled artisan would clearly expect all inherent functions of the α, β, and γ subunits to be present when they are coexpressed in any eukaryotic system and Rothwarf et al. taught means of activating the complex if the complex as produced was not inherently active.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652